

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
3 March 2005 (03.03.2005)

PCT

(10) International Publication Number  
**WO 2005/019223 A1**

(51) International Patent Classification<sup>7</sup>: **C07D 491/22**

(21) International Application Number:  
PCT/CZ2004/000050

(22) International Filing Date: 24 August 2004 (24.08.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
PV 2003-2305 26 August 2003 (26.08.2003) CZ

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Declaration under Rule 4.17:**

— of inventorship (Rule 4.17(iv)) for US only

**Published:**

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD OF MANUFACTURING OF 7-ETHYL-10-[4-(1-PIPERIDINO)-1-PIPERIDINO]-CARBONYLOXY-CAMPTOTHECIN

(57) Abstract: The invention relates to the method of manufacturing of 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxy-camptothecin by condensation of 7-ethyl-10-hydroxycamptothecin with 1-chlorocarbonyl-4-piperidinopiperidine hydrochloride in a polar aprotic solvent in the presence of 4-dimethylaminopyridine.

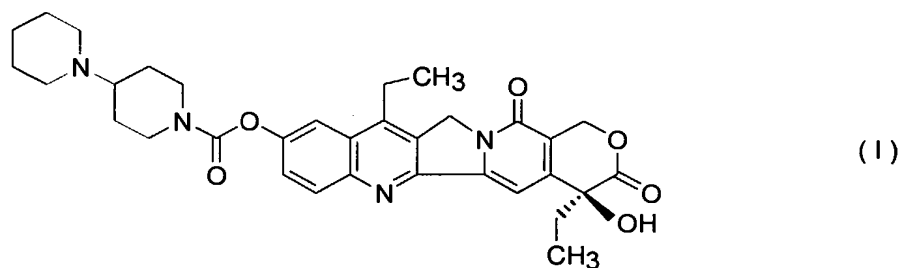


WO 2005/019223 A1

## Method of Manufacturing of 7-Ethyl-10-[4-(1-piperidino)-1-piperidino]- -carbonyloxycamptothecin

### Field of the Invention

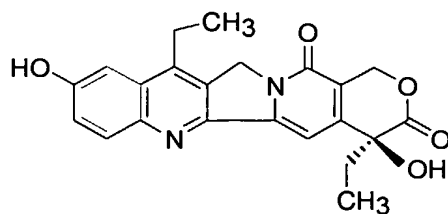
This invention relates to a method of manufacturing of 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxycamptothecin of formula I



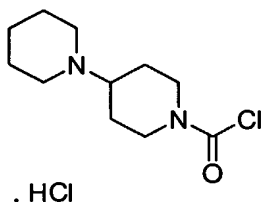
7-Ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxycamptothecin, which is also known as irinotecan base, is used for manufacturing of the cytostatically active irinotecan hydrochloride trihydrate, a topoisomerase inhibitor which is used in treatment of lung and rectum cancer.

### Background of the Invention

7-Ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxycamptothecin has been hitherto prepared by condensation of 7-ethyl-10-hydroxycamptothecin of formula



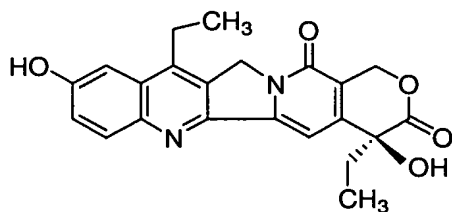
with 1-chlorocarbonyl-4-piperidinopiperidine hydrochloride of formula



in pyridine at room temperature. This method of preparation has been described in US 4 604 463. However, this method of preparation of irinotecan base suffers from the fact that in the condensation coloured impurities are formed which have to be removed by adsorption on a silica gel column and subsequent recrystallization from ethanol. These purification steps are accompanied by substantial losses of the final product and its yields are only about 64 %. Moreover, the method requires distillation of pyridine, extraction of a chloroform layer with sodium carbonate and sodium chloride solutions, and drying of the chloroform layer over magnesium sulfate. Therefore, a better method of preparation of irinotecan base was needed. Such a goal has been achieved by the method according to the present invention.

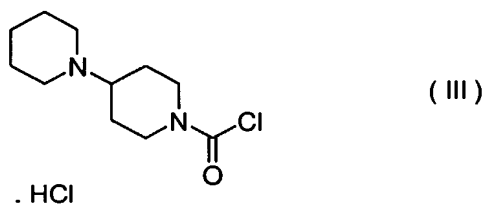
### Summary of the Invention

The present invention relates to a method of manufacturing of 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxycamptothecin of formula I, characterized in that 7-ethyl-10-hydroxycamptothecin of formula II



( II )

is condensed with 1-chlorocarbonyl-4-piperidinopiperidine hydrochloride of formula III



in a polar aprotic solvent such as acetonitrile and in the presence of 4-dimethylaminopyridine. The condensation proceeds in suspension, where the polar aprotic solvent dissolves only 4-dimethylaminopyridine whereas 7-ethyl-10-hydroxycamptothecin and 1-chlorocarbonyl-4-piperidinopiperidine hydrochloride in this polar aprotic solvent remain undissolved. The amount of 1-chlorocarbonyl-4-piperidinopiperidine hydrochloride employed in the condensation reaction is preferably 1.3 to 3 mol, more preferably 1.6 to 1.9 mol, per 1 mol of 7-ethyl-10-hydroxycamptothecin. The amount of 4-dimethylaminopyridine used in the condensation ranges preferably between 1.5 and 4 mol, more preferably between 1.8 and 2.2 mol, per 1 mol of 7-ethyl-10-hydroxycamptothecin. The amount of the polar aprotic solvent used in the condensation is preferably 400 to 600 mol, more preferably 430 to 460 mol, per mol of 7-ethyl-10-hydroxycamptothecin. The condensation is performed preferably at a temperature from 70 to 80 °C, more preferably at 73 to 77 °C.

After end of the condensation, the present ballast compounds, consisting of e.g. 4-dimethylaminopyridine, 4-piperidinopiperidine and urea, are removed by washing of the obtained irinotecan base by a polar aprotic solvent, preferably acetonitrile. The yield of the condensation is at least 94 % and the obtained product contains at least 98 % of the desired irinotecan base, as determined by high-performance liquid chromatography.

The main advantage of the method according to this invention consists in that the work-up of the reaction mixture after condensation proceeds only with negligible losses of the final product and that the condensation is not accompanied with coloured impurities.

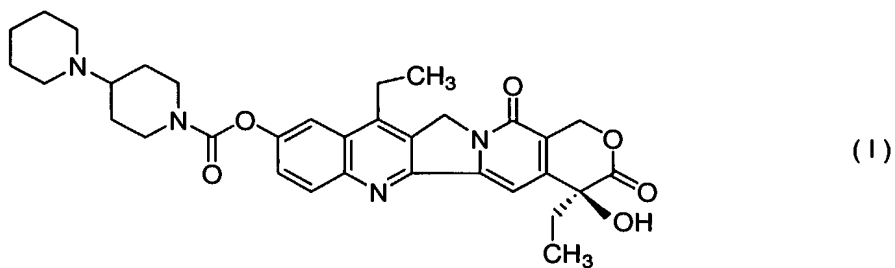
## Examples

### Example 1

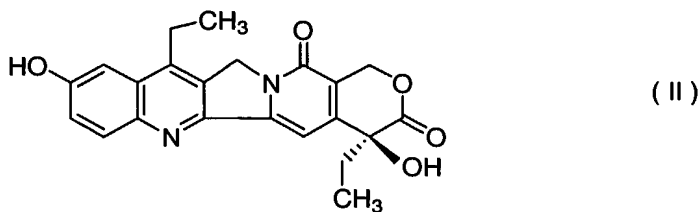
Into a beaker in a sonication bath are placed 10 g (0.0247 mol) of 7-ethyl-10-hydroxycamptothecin and 99 ml of acetonitrile. The obtained suspension is stirred in the sonication bath to homogeneity. Then the suspension is transferred quantitatively into a three-necked Keller flask equipped with a mechanical stirrer, thermometer and reflux condenser. Into the now empty beaker are now placed 6.2 g (0.0502 mol) of crystalline 4-dimethylaminopyridine and 40 ml of acetonitrile. The mixture is stirred until the crystalline portion dissolves. The obtained solution is then added quantitatively to the suspension of 7-ethyl-10-hydroxycamptothecin. Into the empty beaker are then added 13.6 g (0.0434 mol) of 1-chlorocarbonyl-4-piperidinopiperidine hydrochloride and 79 ml of acetonitrile and the suspension is stirred in the sonication bath until homogeneous. The obtained suspension is transferred quantitatively into the three-necked Keller flask already containing 7-ethyl-10-hydroxycamptothecin and 4-dimethylaminopyridine in acetonitrile, and 382 ml of acetonitrile is added to the mixture. The obtained reaction suspension in the Keller flask is stirred at 75 °C for 5 h. After 2 h the lightly yellow suspension becomes thicker and its colour turns into a coffee-white one, indicating thus correct course of the reaction. After 5 h, the suspension is cooled to 18 to 20 °C, filtered and the filtration cake is washed with 300 ml of acetonitrile. After removing the acetonitrile by suction filtration, the obtained 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxycamptothecin is dried at 60 to 65 °C to constant weight in a drier. This affords 14.1 g (yield 94.3 %) of product which, according to high-performance liquid chromatography, contains 98.9 % of 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxycamptothecin.

## PATENT CLAIMS

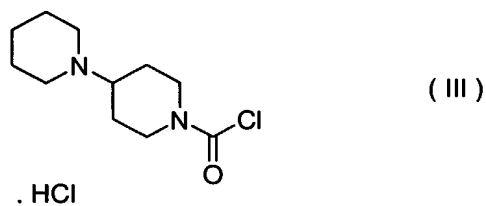
1. A method of manufacturing of 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxy-camptothecin of formula I



characterized in that 7-ethyl-10-hydroxycamptothecin of formula II



is subjected to a condensation reaction with 1-chlorocarbonyl-4-piperidinopiperidine hydrochloride of formula III



in a polar aprotic solvent, e.g. in acetonitrile, in the presence of 4-dimethylaminopyridine.

2. The method according to claim 1, characterized in that 1-chlorocarbonyl-4-piperidinopiperidine hydrochloride is employed in an amount of 1.3 to 3 mol, preferably in an amount of 1.6 to 1.9 mol, per 1 mol of 7-ethyl-10-hydroxycamptothecin.
3. The method according to any of the preceding claims, characterized in that 4-dimethylaminopyridine is employed in an amount of 1.5 to 4 mol, preferably in an amount of 1.8 to 2.2 mol, per 1 mol of 7-ethyl-10-hydroxycamptothecin.
4. The method according to any of the preceding claims, characterized in that the polar aprotic solvent is employed in an amount of 400 to 600 mol, preferably in an amount of 430 to 460 mol, per 1 mol of 7-ethyl-10-hydroxycamptothecin.
5. The method according to any of the preceding claims, characterized in that the condensation reaction is carried out at a temperature of 70 to 80 °C, preferably at a temperature of 73 to 77 °C.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/CZ2004/000050

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 C07D491/22

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SAWADA S ET AL: "SYNTHESIS AND ANTITUMOR ACTIVITY OF 20(S)-CAMPTOTHECIN DERIVATIVES: CARBAMATE-LINKED, WATER-SOLUBLE DERIVATIVES OF 7-ETHYL-10-HYDROXYCAMPTOTHECIN" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 39, no. 6, 1 June 1991 (1991-06-01), pages 1446-1454, XP000653715 ISSN: 0009-2363 the whole document	1-5
X	US 6 235 907 B1 (HENEGAR KEVIN E ET AL) 22 May 2001 (2001-05-22) column 22, line 1 - column 23, line 32 ----- -/--	1-5

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

26 November 2004

Date of mailing of the international search report

03/12/2004

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/CZ2004/000050

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 604 463 A (SUGINO EIICHI ET AL) 5 August 1986 (1986-08-05) example 4 -----	1-4
X	WO 96/31513 A (UPJOHN CO ; HENEGAR KEVIN E (US); SIH JOHN C (US)) 10 October 1996 (1996-10-10) page 31, line 1 - page 32, line 15 -----	1-5

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/CZ2004/000050

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6235907	B1	22-05-2001	US 6444820 B1 03-09-2002
			AT 224899 T 15-10-2002
			AU 717179 B2 16-03-2000
			AU 5527896 A 23-10-1996
			CA 2214793 A1 10-10-1996
			CN 1434044 A 06-08-2003
			CN 1434043 A 06-08-2003
			CN 1434046 A 06-08-2003
			CN 1434037 A 06-08-2003
			CN 1181083 A , B 06-05-1998
			CZ 9703110 A3 18-03-1998
			DE 69623960 D1 31-10-2002
			DE 69623960 T2 05-06-2003
			DK 835257 T3 03-02-2003
			EP 0835257 A1 15-04-1998
			ES 2183943 T3 01-04-2003
			HK 1009448 A1 06-06-2003
			HU 9801436 A2 28-10-1998
			IL 117684 A 10-02-2002
			JP 11503156 T 23-03-1999
			NO 974608 A 08-12-1997
			NZ 306664 A 29-11-1999
			PL 322651 A1 16-02-1998
			PL 186564 B1 30-01-2004
			PT 835257 T 31-01-2003
			RU 2164917 C2 10-04-2001
			SI 835257 T1 30-04-2003
			TW 438775 B 07-06-2001
			WO 9631513 A1 10-10-1996
			US 6121451 A 19-09-2000
			ZA 9602747 A 06-04-1998
US 4604463	A	05-08-1986	JP 1660064 C 21-04-1992
			JP 3004077 B 22-01-1991
			JP 60019790 A 31-01-1985
			AT 33839 T 15-05-1988
			CA 1235415 A1 19-04-1988
			DE 3470744 D1 01-06-1988
			DE 137145 T1 21-11-1985
			EP 0137145 A1 17-04-1985
			LU 90074 A9 21-08-1997
			NL 980026 I1 02-11-1998
WO 9631513	A	10-10-1996	AT 224899 T 15-10-2002
			AU 717179 B2 16-03-2000
			AU 5527896 A 23-10-1996
			CA 2214793 A1 10-10-1996
			CN 1434044 A 06-08-2003
			CN 1434043 A 06-08-2003
			CN 1434046 A 06-08-2003
			CN 1434037 A 06-08-2003
			CN 1181083 A , B 06-05-1998
			CZ 9703110 A3 18-03-1998
			DE 69623960 D1 31-10-2002
			DE 69623960 T2 05-06-2003
			DK 835257 T3 03-02-2003
			EP 0835257 A1 15-04-1998
			ES 2183943 T3 01-04-2003

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/CZ2004/000050

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9631513 A		HK 1009448 A1	06-06-2003
		HU 9801436 A2	28-10-1998
		IL 117684 A	10-02-2002
		JP 11503156 T	23-03-1999
		NO 974608 A	08-12-1997
		NZ 306664 A	29-11-1999
		PL 322651 A1	16-02-1998
		PL 186564 B1	30-01-2004
		PT 835257 T	31-01-2003
		RU 2164917 C2	10-04-2001
		SI 835257 T1	30-04-2003
		TW 438775 B	07-06-2001
		WO 9631513 A1	10-10-1996
		US 6121451 A	19-09-2000
		US 6235907 B1	22-05-2001
		US 6444820 B1	03-09-2002
		ZA 9602747 A	06-04-1998

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